and further wherein the vitamin $D_3$ derivative is

(i) (20S)-1α, 25-dihydroxy-2β-methyl-3β-vitamin $D_3$;

(ii) (20S)-1β, 25-dihydroxy-2β-methyl-3α-vitamin $D_3$;

(iii) (20S)-1α, 25-dihydroxy-2α-methyl-3β-vitamin $D_3$; or

(iv) (20S)-1α, 25-dihydroxy-2α-methyl-3α-vitamin $D_3$. --

## REMARKS

New Claims 3 and 4 are all the claims pending in the application for the Examiner's further consideration. Claims 1 and 2 have been canceled, and new Claims 3 and 4 find support, *inter alia*, in canceled Claims 1 and 2, respectively.

The specification at page 32 has been amended to correct inadvertent typographical errors in the synthesis reaction depicted in Example 1. Specifically, the stereochemistry of the 2-position methyl group in compound nos. (42), (80) and (72) has been reversed from a downward position to an upward position. Support for the amending of the 2-position is found in compound (42) on page 30 of the specification.

Additionally, the stereochemistry of the 20-position methyl group in compound nos. (80) and (72) has been changed from an R-form to an S-form, as has the corresponding position in the starting material, compound (92). Applicants submit that the amendment would be obvious to one of ordinary skill in the art based on the structure of formula (I).

No issue of new matter should be raised, and entry of the amended specification and new claims is requested.

## I. Withdrawal of the Objections to Claims 1-2

The Examiner has acknowledged the Amendment of December 30, 1999, and the amendments to Claims 1-2 have been entered and are of record. Accordingly, the Examiner has withdrawn the objections to these claims.

## II. Response to Objection to the Declaration under 37 C.F.R. § 1.132

The Examiner for the following reasons has objected to the Declaration filed with the Amendment of December 30, 1999:

**1.** The Examiner is requesting that Applicants provide an executed version of the same declaration.

The executed Declaration under 37 C.F.R. § 1.132 of Mr. Ishizuki is enclosed herewith, thereby obviating the Examiner's objection.

**2.A.** According to the Examiner, the Declaration does not clearly indicate which of the compounds are being compared as there should be a side-by-side comparison under MPEP §716.02(e).

Applicants respectfully submit that under the section entitled "Conclusion", the comparative compounds are clearly set forth as being (4) versus (72); (65) versus (68); (6) versus (74); and (3) versus (71) which is comparative and which is inventive because 4 can be comparative and 72 inventive or vice versa. However, to advance prosecution, a Supplemental Declaration under 37 C.F.R. § 1.132 is enclosed herewith, containing a newly organized table with a side-by-side comparison of the 20S and 20R compounds.

**2.B.** The Examiner further indicates that the declaration does not describe the actual compound to which each of the numbers refers.

To satisfy the Examiner's request, a footnote has been added to the table in the Supplemental Declaration, indicating where written description support can be found in the specification for the chemical structures to each of the compounds. In this respect, the chemical structures for the compounds find support in the specification as follows:

**20S forms (inventive compounds):**

Compound 68: Example 2, page 33

Compound 71: Example 5, page 36

Compound 72: Example 1, page 32

Compound 74: Example 7, page 37

**20R forms (reference compounds):**

Compound 3: page 39, line 30

Compound 4: page 39, line 31

Compound 6: page 39, line 33

Compound 65: page 40, line 1

## III. Response to Objection to the Specification

In the Office Action of June 30, 1999, the Examiner raised an objection to the data presented on page 39 of the specification[1]. Applicants responded by filing the Declaration of

[1] Example 9 on page 39 of the specification was objected to by the Examiner for allegedly not convincingly demonstrating a significant difference in the activity for 20S forms of the derivatives compared to the 20 R forms.

December 30, 1999, however, this objection is outstanding in view of the fact that entry of the Declaration has been denied. The Supplemental Declaration addresses this point, and overcomes the objection.

## IV. Examiner's Additional Comments

Applicants are not able to clearly discern the issue raised by the Examiner under the third point on page 3 of the Office Action.

If the Examiner's objection relates to the arguments filed in the Amendment of December 30, 1999, which are based on evidence in the unentered Declaration, then the newly organized Supplemental Declaration should resolve the outstanding issue(s). In the event the Supplemental Declaration does not address this issue, the Examiner is requested to further clarify his position.

## V. Response to Rejection of Claim 1 under 35 U.S.C. § 103(a)

Claim 1 is rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Miyamoto et al. (U.S. Patent 5,877,168) as set forth in paper no. 4.

According to the Examiner, Miyamoto discloses triethylsilyloxy vitamin D derivatives with 2β-position substituents (generally, the entire document; specifically, at col. 2, lines 33-42 and example 14) having in vitro calcium regulatory activity, differentiation stimulating activity on tumor cells, and use in the treatment of osteoporosis.

The Examiner states and concludes that the instant claims which cover tri$C_1$-$C_7$alkylsilyloxy vitamin D, are broader in scope than the derivatives of Miyamoto but that it would have been *prima facia* obvious to modify the instant compounds to obtain compounds having the same properties as those of Miyamoto.

Applicants submit that the Examiner's rejection of Claim 1 is moot in view of the cancellation of the claim. New Claim 3 is drawn to only those compounds (compounds 68, 71, 72 and 74) which exhibit unexpectedly superior biological properties compared to the reference compounds, and therefore, should not raise an issue under §103(a).

Applicants further submit, that the unexpectedly superior results (i.e., high affinity for the vitamin D receptor (compounds 68 and 72) or high differentiation induction effect on the HL-60 cell line (compounds 68, 71, 72 and 74)) were previously demonstrated in the Declaration of Mr. Ishizuka, and that these observations are resubstantiated in the Supplemental Declaration of Mr. Ishizuka enclosed herewith. Accordingly, withdrawal of the rejection is requested.

## VI. Response to Rejection of Claim 2 under 35 U.S.C. § 103(a)

Claim 2 is rejected under 35 U.S.C. § 103(a) as being obvious over Trost et al. (J.Am.Chem.Soc. Vol. 114, pages 9836-45, 1992) as set forth in paper no. 4.

The Examiner concludes that whereas the starting material in the synthesis reaction for the vitamin D derivatives of the instant process claims is different from the starting material used in the Trost reaction, the materials are chemical analogues, i.e., both are enynes of formula III. Accordingly, the Examiner concludes that it would have been *prima facia* obvious to substitute the enynes of Trost with the instant starting material to obtain a compound having similar properties.

Applicants submit that the Examiner's rejection of Claim 2 is moot in view of the cancellation of Claim 2. New Claim 4 is drawn to the synthesis pathway for only those compounds (compounds 68, 71, 72 and 74) which exhibit unexpectedly superior biological

properties compared to the reference compounds, and therefore, should not raise an issue under §103(a).

Accordingly, withdrawal of the rejection is requested.

## VII. Response to Rejection of Claims 1-2 for obviousness-type double patenting

Claims 1 and 2 are provisionally rejected for obviousness-type double patenting in view of Claims 1 and 2 of USAN 09/068,219 ('219).

According to the Examiner, instant Claims 1 and 2 are obvious in view of the similarity of the claimed subject matter to Claims 1 and 2 of Applicants' '219 application which are directed to 2-substituted vitamin D analogues having R as tri($C_1$-$C_7$ alkyl)silyl derivative.

Applicants submit that the Examiner's rejection is moot in view of the cancellation of Claims 1 and 2.

With respect to the claimed compounds of the instant application and those of the '219 application, Applicants direct the Examiner's attention to a notable, patentable distinction; the stereochemistry at the 20 position of the vitamin $D_3$ derivatives. The only claimed derivatives for the instant application are of an S form, whereas the derivative in Applicants' '219 application is directed to only an R form.

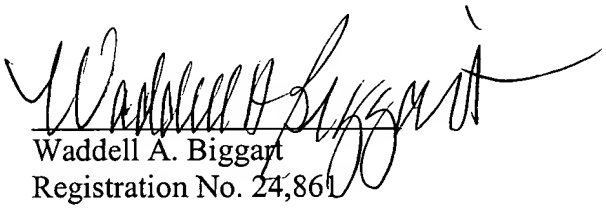
In view of the directing of the instant claims to S-form derivatives, and to those which exhibit unexpectedly superior receptor binding properties, the claimed subject matter, is therefore, nonobvious over the claimed subject matter of the '219 application.

## CONCLUSION

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such action is hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Applicants hereby petition for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,



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